

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference X16080	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/007052	International filing date (<i>day/month/year</i>) 08/03/2005	(Earliest) Priority Date (<i>day/month/year</i>) 12/03/2004
Applicant ELI LILLY AND COMPANY		
<p>This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.</p> <p>This International Search Report consists of a total of <u>3</u> sheets.</p> <p><input checked="" type="checkbox"/> It is also accompanied by a copy of each prior art document cited in this report.</p>		
<p>1. Basis of the report</p> <p>a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.</p> <p><input type="checkbox"/> The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).</p> <p>b. <input type="checkbox"/> With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.</p> <p>2. <input type="checkbox"/> Certain claims were found unsearchable (See Box II).</p> <p>3. <input type="checkbox"/> Unity of invention is lacking (see Box III).</p> <p>4. With regard to the title,</p> <p><input checked="" type="checkbox"/> the text is approved as submitted by the applicant.</p> <p><input type="checkbox"/> the text has been established by this Authority to read as follows:</p>		
<p>5. With regard to the abstract,</p> <p><input checked="" type="checkbox"/> the text is approved as submitted by the applicant.</p> <p><input type="checkbox"/> the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.</p> <p>6. With regard to the drawings,</p> <p>a. the figure of the drawings to be published with the abstract is Figure No. _____</p> <p><input type="checkbox"/> as suggested by the applicant.</p> <p><input type="checkbox"/> as selected by this Authority, because the applicant failed to suggest a figure.</p> <p><input type="checkbox"/> as selected by this Authority, because this figure better characterizes the invention.</p> <p>b. <input type="checkbox"/> none of the figures is to be published with the abstract.</p>		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/007052

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D409/12 C07D405/12 C07D307/91 C07D491/04 A61K31/335
A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	✓ EP 0 569 802 A (MERCK PATENT GMBH) 18 November 1993 (1993-11-18) the whole document -----	1-21
A	✓ US 4 678 779 A (MEYERS ET AL) 7 July 1987 (1987-07-07) the whole document -----	1-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

11 August 2005

Date of mailing of the international search report

22/08/2005

Name and mailing address of the ISA

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Authorized officer

Grassi, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/007052

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 0569802	A	18-11-1993	DE AT AU BR CA CN CZ DE DK EP ES HK HU JP JP NO PL RU SK US ZA	4215213 A1 168368 T 3834193 A 1100581 A3 2095797 A1 1079219 A ,C 9300823 A3 59308763 D1 569802 T3 0569802 A1 2121030 T3 1011990 A1 70172 A2 3210771 B2 6049022 A 931681 A ,B, 298845 A1 2125041 C1 46893 A3 5532266 A 9303222 A	11-11-1993 15-08-1998 11-11-1993 01-08-2000 10-11-1993 08-12-1993 16-02-1994 20-08-1998 19-04-1999 18-11-1993 16-11-1998 24-03-2000 28-09-1995 17-09-2001 22-02-1994 10-11-1993 10-01-1994 20-01-1999 06-04-1994 02-07-1996 08-12-1993	11-11-1993 15-08-1998 11-11-1993 01-08-2000 10-11-1993 08-12-1993 16-02-1994 20-08-1998 19-04-1999 18-11-1993 16-11-1998 24-03-2000 28-09-1995 17-09-2001 22-02-1994 10-11-1993 10-01-1994 20-01-1999 06-04-1994 02-07-1996 08-12-1993
US 4678779	A	07-07-1987	US	4910152 A		20-03-1990

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X 16080

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

12 DEC 2005 / 12 JAN 2006

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No. PCT/US2005/007052	International filing date (day/month/year) 08.03.2005	Priority date (day/month/year) 12.03.2004
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International Patent Classification (IPC) or both national classification and IPC
C07D409/12, C07D405/12, C07D307/91, C07D491/04, A61K31/335, A61P3/04

Applicant

ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/007052

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - in written format
 - in computer readable form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application,
 claims Nos. 16-20

because:

- the said international application, or the said claims Nos. (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 no international search report has been established for the whole application or for said claims Nos.
 the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- has not been furnished
 does not comply with the standard

the computer readable form

- has not been furnished
 does not comply with the standard

- the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

- See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/007052

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-15,21
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: EP-A-0 569 802

Re Item III

Claims 15-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

- 1) The subject-matter of present claims 1-21 is new (Article 33(2) PCT).
- 2) The subject-matter of claims 1-21 involves an inventive step (Article 33(3) PCT).

The closest prior art is represented by D1 relating to compounds with affinity to the kappa receptor. The most relevant compounds of D1 are the xanthene derivatives disclosed in example 5.

The present compounds differ from the compounds of D1 in the two mandatory substituents on the tricyclic ring system.

The technical problem underlying the present application is seen in the provision of alternative agents having affinity to opioid receptors.

In view of the test results disclosed on the pages 22/23, the problem appears to be solved.

The prior art does not appear to prompt the skilled person to the presently claimed compounds. Consequently, inventive activity appears to be involved.

Therefore, the subject-matter of the claims relating to a pharmaceutical composition or to the use of the compounds also fulfill this requirement.

REMARK

- 1) Several examples (e.g. examples 8-12 or 15-19) appear not to fall within the generic definition of claim 1 (with respect to residues R1/R2).
 - 1.1) The same applies to several residues mentioned in dependent claim 11.
- 2) The term prodrug does not satisfy the requirements of Article 6 PCT. The term is to be seen as a functional feature. Functional features are, however, allowable only if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to a person skilled in the art and which do not require undue experimentation (cf. Guidelines, II, 5.35).